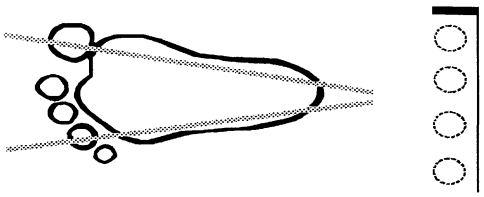
NEWBORN SCREENING



December 2001

Be Kind To Tiny Feet

A newsletter of the Newborn Screening Program and the Newborn Screening Laboratory

HEMOGLOBINOPATHIES

Third Edition

The genetics of hemoglobinopathy newborn screening
Last edition in a three part series on hemoglobinopathies

EDITOR'S CORNER

Whoops!

I know-bad word for the medical profession! I forgot to print this acknowledgement in the last newsletter. The Utah State Laboratory is screening for hemoglobinopathies using isoelectric focusing (IEF). How the IEF instruments work was explained in the First Edition (published April 2001). I would like to introduce to you-David Biggs, BS-who is the Microbiologist responsible for operating the isoelectric instruments. David has been working under the direction of Barbara Jepson, MT, ASCP to set-up the IEF lab and is now responsible for all the newborn screening for hemoglobinopathis. David graduated from Brigham Young University. He is married and has seven children. David has been working in Newborn Screening at the State Lab since 1979 (the year Utah began the newborn screening program). David is excited about his new role in newborn screening. I believe that David is dedicated, hard working, and will be a valuable team member for hemoglobinopathy screening.

David Biggs has had help from a summer intern, David Tomer. David Tomer is a recent graduate in microbiology from BYU with a specialty in Molecular Biology. David (the intern) navigated through several forms of complex software to develop the method that will be used to scan and quantitate the screening hemoglobin bands.

Thank you to the David team! **Jan Bagley, RN**

Confirmed Hemoglobin Traits

As of December 1, 2001 (screening for hemoglobinopathies started on September 24, 2001) the Utah Department of Health has confirmed the following hemoglobin traits: 9 infants with FAS (Sickle Cell Trait), 3 infants with FAE (Hemoglobin E Trait), and 5 infants with FAU (Unidentified Trait bands; possible alpha globin variants). There are 26 presumptive abnormal first screenings in the process of being confirmed.

Utah Department of Health

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Division of Epidemiology & Laboratory Services, Newborn Screening Laboratory: (801) 584-8400 fax: (801) 584-8486

GENETIC FOLLOW-UP FOR HEMOGLOBINOPATHIES

Laurel K. Berkheim, MS, Genetic Counselor
David H. Viskochil, MD, Medical Geneticist

The primary purpose of newborn screening for hemoglobinopathies is the identification of individuals affected with a clinically significant sickle cell disease (SCD) or thalassemia. These chronic conditions have a significant impact on the families and the health care system because of the prevalence of the conditions and the treatment they require. About one in 400 African-American newborns have SCD and 8%, or one in 12 African-Americans, is a carrier for sickle cell trait. The main populations at risk for hemoglobinopathies include those of African, Mediterranean, Middle Eastern, Indian, Caribbean, and South or Central American descent. Utah's demographics are changing to include more representatives from these populations. According to the July 2000 census report, 10% of Utah's population is a member of an ethnic or racial minority (1% African-American, 2.9% Asian or Pacific Islander, and 6.5% Hispanic).

Universal screening for hemoglobinopathies was recommended following an NIH Consensus Development Conference in 1987. This recommendation was made because neonatal screening identifies those with SCD early, allowing them to receive comprehensive health care. These infants receive early intervention with Penicillin prophylaxis, which significantly decreases morbidity and mortality due to sepsis in infants with SCD.

Genetics of Sickle Cell Disease and Hemoglobinopathies

The hemoglobin molecule consists of two types of polypeptide chains (two each of both chains). In normal adult hemoglobin, these chains are α (alpha) and β (beta). There are two genes that are important for the production of adult hemoglobin. The *α-globin* gene is located on chromosome 16 and the *β-globin* gene is located on chromosome 11. Many different types of defects can occur in these genes to cause a hemoglobinopathy, as outlined in figure 1. There are over 600 hemoglobin variants and they demonstrate the broad biologic mechanisms underlying genetic disorders. Many hemoglobinopathies have little or no clinical significance, but some are associated with significant medical problems. (See the first and second editions of the hemoglobinopathy newsletters for more details about clinical significance).

Generally, thalassemias are a result of an imbalance in the production of either the α-globin or β-globin chain. Alpha-thalassemia results from deletions in the *α-globin* genes leading to loss of function and subsequent reduction in gene dosage and α-globin product. Likewise, β-thalassemia is due to reduced production of β-globin. However, the gene defect in β-thalassemia is more often a single base-pair substitution than a deletion and it generally affects either β-globin chain production or integrity. The end result of either thalassemia is a reduced amount of hemoglobin due to the deficiency of one of the globin chains.

Sickle cell disease encompasses a group of symptomatic disorders characterized by predominance of sickled red blood cells. There are four main genotypes that result in clinically significant disease, although there are several genotypes associated with

varying degrees of microcytosis (small red blood cells) and/or anemia.[1]

Sickle cell diseases are caused by mutations in *the β-globin* gene. Hemoglobin S (Hb "S" represents Sickle) is the most common hemoglobin variant that causes SCD. Hemoglobin S is caused by a base substitution in the *β-globin* gene leading to a single amino acid substitution in the β-globin polypeptide, which alters the function of hemoglobin. Everyone with Hb S shares this same gene mutation. A thymine replaces an adenine in the DNA encoding for the *β-globin* gene. Consequently, the amino acid valine replaces glutamic acid at the sixth position in the *β-globin* protein product.

Sickle cell disease is caused by mutations in both copies of the *β-globin* gene. This can be a combination of Hb S, Hb C, or beta thalassemia (and occasionally other more rare variants). SCD is inherited in an autosomal recessive manner. A child can inherit sickle cell disease only if both parents are carriers for one sickle cell gene variant (or trait). If both parents are carriers, with each pregnancy there is a 25% chance of having a child with sickle cell disease, a 50% chance the child would be a carrier, and a 25% chance the child would not have any mutations. (Figure 2)

Genetic Services for Hemoglobinopathies

Patients with clinically significant disease should receive comprehensive care from medical professionals knowledgeable about hemoglobinopathies. Education, genetic counseling, and screening for family members should be offered to all families of individuals who are identified by newborn screening with SCD. Genetic evaluation and counseling should include comprehensive evaluation of the family history. A complete explanation of autosomal recessive inheritance and accurate, non-directive counseling for reproductive risks should be provided. Additionally, discussion of screening other family members who are at risk for a hemoglobinopathy is needed. The evaluation may also include explanation of SCD and the disease process, psychosocial support, and appropriate referral to support services.

Genetic Services for Traits

Identifying carriers for a hemoglobin trait is a byproduct of the newborn screening test. Approximately 50 infants who are carriers of hemoglobin traits are identified for every one infant with sickle cell disease.[1] Parents of all infants who are detected to be carriers of hemoglobin traits should be offered appropriate education, genetic counseling, and hemoglobinopathy screening for themselves and their extended family.[1]

Most carriers do not have anemia and do not require treatment or restrictions on physical activity. However, some variants may be associated with clinical manifestations, even in heterozygotes. Other variants have no clinical consequences in either heterozygous or homozygous individuals, but may cause SCD when co-inherited with Hb S and thus have potential clinical and genetic implications.[2]

Carriers of hemoglobinopathies are usually normal. About 5% of carriers have hematuria at some time and most cannot concentrate their urine, but these are generally clinically insignificant abnormalities. Under extreme circumstances such as altitude hypoxia,

acidosis, severe dehydration, and hypothermia, carriers can have medical complications. Although low, the risk of sudden unexplained death associated with exercise in Hb S carriers is higher than in non-carriers.[3] The potential for complications in sickle cell trait deserve full discussion with those family members who prove to be carriers.

Potential benefits of genetic counseling for carrier status include: 1. Informed, future reproductive choice for both the parents and for the child. 2. Education about the clinical implications of carrier status. 3. Helpful discussions with the parents to distinguish between carrier and disease status.[4] Genetic counseling enables parents and other family members to make informed choices about hemoglobin screening. Screening could help to identify couples with sickle cell trait who are at risk for having future children with SCD.

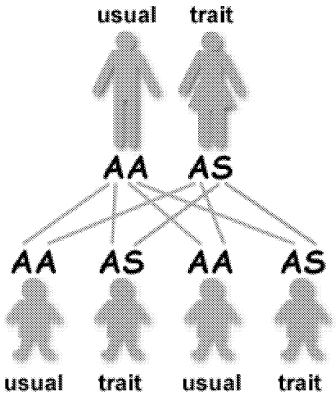
Some families might choose to pursue further testing to clarify reproductive risks. Testing of potential carriers, such as the parents of a carrier child, requires a CBC (complete blood count with red blood cell indices) and hemoglobin electrophoresis. It should be noted that testing the parents might reveal non-paternity issues. Testing should ***not*** be performed without discussion with the parents and their consent.

Resources

1. Sickle Cell Disease Assoc. of America
   http://www.sicklecelldisease.org
   (800) 421-8453
2. Cooley's Anemia Foundation
   http://www.thalassemia.org/
3. http://sickle.bwh.harvard.edu
4. GeneReviews (formerly GeneClinics)
   Beta-Thalassemia—www.genetests.org

References

1. Pass et al. US Newborn screening system guidelines II: follow-up of children, diagnosis, management, and evaluation statement of the council of regional networks for genetic services. J Pediatr 2000; 137(Suppl): S1-S46.
2. Shafer et al. Newborn screening for sickle cell disease: 4 years of experience from California's newborn screening program. J Pediat Hematol/Oncol 1996; 18:36-41.
3. Kark J. Sickle cell trait. http://sickle.bwh.harvard.edu/sickle_trait.html
4. Laird L, Dezateux C, and Anionwu EN.Neonatal screening for sickle cell disorders: what about the carrier infants? BMJ 1996; 313; 407-411



- If one parent has sickle cell trait there is a 50% chance with each pregnancy of having a child with sickle cell trait.

THANK YOU-to the New York State Department of Health, Newborn Screening Program-who provided us with "The Family Connection," Sickle Cell Trait and Hemoglobin C Trait educational brochures. The pamphlets will be a valuable addition to our hemoglobinopathy follow-up educational materials. "You get by with a little help from your friends."

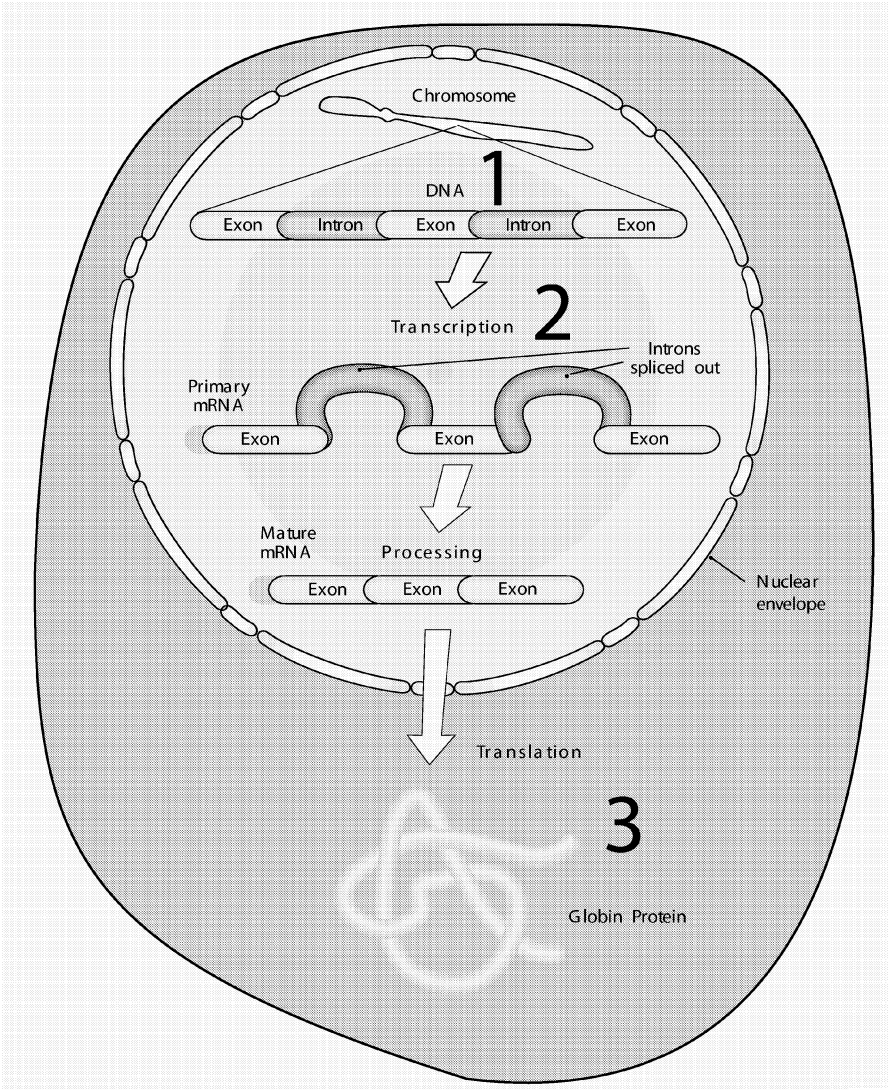


Figure 1. Many different gene defects cause hemoglobinopathies and can disrupt the formation of a complete protein at one of many steps in the process of hemoglobin synthesis.

1. Large deletions in the DNA cause thalassemias by decreasing production of mRNA and thus decreased protein.
2. Non-functional mRNA's due to nonsense or frameshift mutations in the gene cause errors in translation and also lead to thalassemias.
3. Sickle cell disease and other variants affect protein structure and/or function. mRNA levels are usually normal.

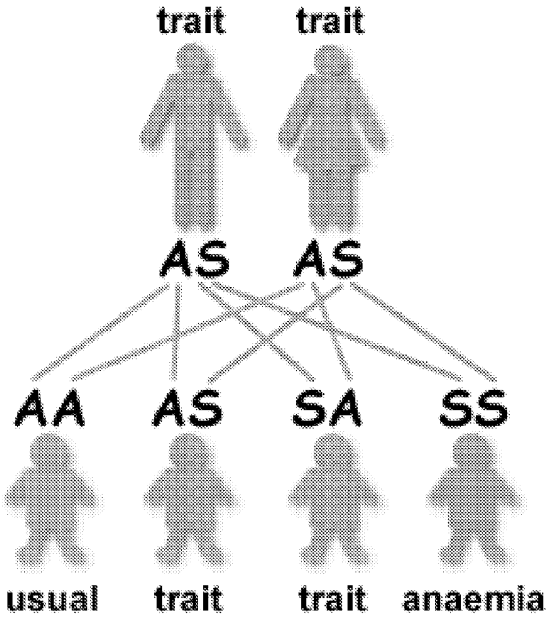


Figure 2. Inheritance of sickle genes from parents with sickle cell trait. The A is the normal gene and the S stands for the mutation in the β-globin gene. Each parent carries one β-globin gene abnormality for sickle cell disease (AS) and randomly passes on one of their number 11 chromosomes which harbors one β-globin gene. On average, the couple has one chance in four (25%) that the child will be normal, one chance in four (25%) that the child will have sickle cell disease, and one chance in two (50%) that the child will have sickle cell trait (be a carrier like his or her parents).

Genetic Terms Defined

ALLELE – One of two or more different genes containing specific inheritable characteristics.

AUTOSOMAL RECESSIVE – Requires that both parents carry traits for the gene in order for it to be passed to their offspring. If both parents carry the gene (heterozygous) then there is a one in four chance, with each pregnancy, of having an offspring with the complete disease and a 50% chance of the child being at least a carrier (heterozygous—like the parents). (See figure 2)

CARRIER – A person who does not have a hemoglobinopathy but carries a recessive gene with a normal gene. A carrier is capable of transmitting the disease.

GENE– The basic unit of heredity.

GENETICS – Is the study of how similarities are inherited from your parents**.**

HETEROZYGOUS – Possessing different alleles at a given locus. (Sickle Cell Trait)

HOMOZYGOUS – Produced by similar alleles. (Sickle Cell Disease)

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